

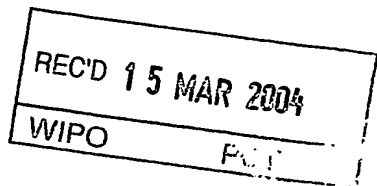


PCT/GB 2004 / 0 0 0 7 2 6

23 FEBRUARY 2004

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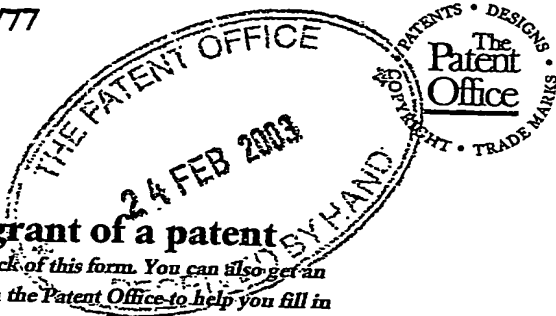
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25FEB03 E787343-18002093
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The Patent Office

Cardiff Road
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1. Your reference

PPD 70229/GB/P

2. Patent application number

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0304132.4

24 FEB 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SYNGENTA Limited
European Regional Centre
Priestley Road
Surrey Research Park, Guildford,
Surrey, GU2 7YH, United Kingdom

Patents ADP number (if you know it)

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

08 330748001

4. Title of the invention

CHEMICAL PROCESS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

John Richard WATERMAN
Intellectual Property Department
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PO Box 3538
Bracknell, Berkshire, RG42 6YA
UNITED KINGDOM

Patents ADP number (if you know it)

06 791537002

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Country

Priority application number
(if you know it)

Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
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Claim(s) 01✓ *2/1/1*

Abstract 01✓

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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11.

I/We request the grant of a patent on the basis of this application.
Syngenta Limited

Signature *M A Rudd*
Authorised Signatory

Date *24/2/03*

12. Name and daytime telephone number of person to contact in the United Kingdom

Margaret Ann RUDD – 01344 413673

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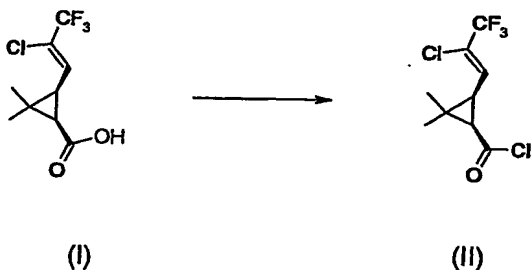
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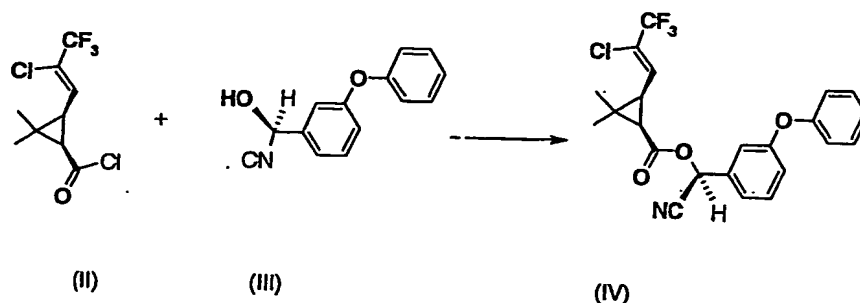
CHEMICAL PROCESS

The present invention relates to a process for making insecticidal
 5 cyclopropanecarboxylic acid esters. More particularly, the invention relates to a
 process for making gamma-cyhalothrin [(S)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-
 (2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate].

It is well known that the insecticidal activity of pyrethroids such as
 cyclopropanecarboxylic acid esters e.g. cyhalothrin is greatly affected by their
 10 stereochemistry. It is disclosed in Bentley et al, Pestic.Sci. (1980), 11(2), 156-64) that
 (S)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-
 2,2-dimethylcyclopropanecarboxylate is the most active isomer of cyhalothrin.

In order to produce gamma-cyhalothrin on an industrial scale it is desirable to
 find methods of making the final product that avoid the use of expensive reagents and
 15 have as few chemical stages as possible. The present invention provides a direct
 process to meet these requirements. There is therefore provided a process for the
 preparation of gamma-cyhalothrin (IV) comprising a) chlorinating 1R *cis*-Z 3-(2-
 chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid (I) to
 give 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl
 20 cyclopropanecarboxylic acid chloride (II) and b) esterifying 1R *cis*-Z 3-(2-chloro-
 3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid chloride (II)
 with the (S)-cyanohydrin of 3-phenoxy benzaldehyde (III).





1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl
cyclopropanecarboxylic acid (I) is a known compound and its preparation is described
5 for example in US4683089, WO02/06202, WO97/03941 and WO/9942432.

Step a) is performed by standard techniques as in '*March 4th Edition - p437-38*'. Preferred chlorinating agents are thionyl chloride, phosgene or phosphorous
oxychloride. Preferred solvents are hydrocarbons such as toluene, hexane, heptane or
fluorobenzene. Preferred temperatures are from ambient to 100°C or the boiling point
10 of the solvent.

Preferably the acid (I) has an enantiomeric purity of greater than 80% of 1R 3R
enantiomer, and more preferably greater than 90% 1R 3R enantiomer.

Step b) is performed in the presence of a solvent or in the absence of a solvent,
in which case the molten product can act as the reaction medium. The reaction can be
15 carried out in a single organic phase or in a mixture of a water immiscible organic
phase and an aqueous phase. The acid chloride, either neat or in a solvent, may be
added to the cyanohydrin, or the vice versa, but it is preferable to add the acid chloride
to the cyanohydrin. The mol ratio of the reactants is preferably 1:1 but up to 10mol %
excess of either reactant can be employed, but most preferably the excess of one
20 reactant over the other is 1-5mol%.

On an industrial scale it is highly desirable that the reaction is taken to
completion (where, in the case of 1:1 stoichiometry of reactants, completion means
there is a residual level of both acid chloride and cyanohydrin of <5% by weight and
preferably <1% by weight, and where one reactant is used in excess of the other, the
25 residual level of the minor reactant is <1% preferably <0.2%) to maximize the yield.

In known esterification processes taking the reaction to completion has been
attempted either by performing the reaction in the presence of a stoichiometric amount
of an organic base (US4258202) or by physical removal of the HCl as it is formed by

conducting the reaction at the boiling point of the solvent (US5164411). However neither of these processes is satisfactory. The use of stoichiometric amounts of a base is undesirable as this necessitates a complicated recovery process to avoid the cost of disposing of the base. When using physical removal of HCl as a means of progressing the esterification reaction, the applicants have found that it is difficult to consume the last few % of the reactants without significantly extending the reaction time. Surprisingly the reaction can be taken to completion within an acceptable time by removal of HCl from the reaction using a combination of physical methods and a sub-stoichiometric amount of a base.

Therefore in one embodiment of the invention there is provided a process in which HCl formed during the esterification is removed from the reaction mass using a combination of physical methods and a sub-stoichiometric amount of a base.

Physical removal of co-product HCl can be accomplished by conducting the reaction at the boiling point of the solvent or by continuous removal of the solvent by distillation whilst adding fresh solvent to replace that which has been distilled out or by application of vacuum or by sparging the reaction mass with an inert gas such as nitrogen or by the presence of a separate water phase that can extract the HCl, or by any combination of these procedures. The base can be either an organic base, such as a tertiary amine, or an inorganic base such as an alkali metal carbonate or bicarbonate or alkaline earth metal oxide, hydroxide or carbonate or a combination of an organic and an inorganic base. In the latter case, the organic base serves to facilitate the reaction of the HCl formed in the reaction with the heterogeneous inorganic base.

The base may be added from the outset or may be added during the course of the reaction but is preferably added once the reaction has been taken to >50% by physical removal of HCl and most preferably after the reaction is >80% completed. The applicants have found that addition of the base late on in the reaction has the advantage of minimising impurity formation and maximizing yield.

Preferred organic bases have a pKa of between 2 and 7 and more preferably between 3 and 6. Particularly preferred organic bases are pyridine, alkylpyridines, quinoline, the trimethylether of triethanolamine or the mono-hydrochloride salt of DABCO. The base can be used at <0.8 equivalents on the acid chloride, preferably

<0.5 equivalents and most preferably between 0.1-0.25 equivalents. When an organic and an inorganic base are combined, it is desirable to have the inorganic base as the major component of the binary mixture and the organic base as the minor component.

5 Thus the organic base is preferably <50% and most preferably <10% of the total molar amount of base used in the reaction.

Suitable solvents for the reaction are aliphatic or aromatic hydrocarbons.

Examples of aromatic hydrocarbons are toluene, o-xylene, mixed xylenes or halobenzenes, for example fluorobenzene. Aliphatic hydrocarbons are for example
10 hexane, cyclohexane, iso-hexane, heptane, octane or mixtures of hydrocarbons commonly known as petroleum ethers. Preferred solvents are hexane, cyclohexane, iso-hexane, heptane or octane. In a preferred embodiment of the invention, the same solvent is used in both steps a) and b). Suitable temperatures for the reaction are in the range 20-120°C, preferably 60-80°C.

15 In a further aspect of the invention, the esterification can be carried out in a two-phase system in which one phase is an aqueous phase and optionally in the presence of an organic base that may act as a reaction promoter. The aqueous phase serves to help extract the HCl as it forms from the organic phase and the pH of the aqueous phase can be maintained at a desired level by addition of base to neutralize
20 the HCl as it forms. The preferred pH of the aqueous phase is pH 3-10 but preferably pH 6-8. The pH can be maintained by continuous addition of an inorganic base, for example sodium or potassium hydroxide, and the use of a 'pH stat', which will control the pH automatically. The pH control is optionally carried out in the presence of a buffer, which helps to avoid large swings in the pH. Suitable buffers are borate or
25 phosphate salts. Suitable reaction promoters are organic bases such as pyridine or alkyl pyridines.

On completion of the reaction, any base, along with salts formed in the reaction, can be removed by washing the product with dilute mineral acid. Optionally this can be carried out at elevated temperature to hydrolyse any residual acid chloride,
30 or any acid anhydride formed in the reaction, to the carboxylic acid. The carboxylic acid can then be removed from the product by washing with water that has a pH maintained in the region of pH 5-8 and preferably pH 6-7. This can be accomplished

by the use of an appropriate buffer and controlled addition of a base, for example sodium or potassium dihydrogen phosphate and sodium or potassium hydroxide. Finally, the product is washed with dilute acid to prevent epimerisation at the benzylic position and any solvent is removed by conventional methods. The product can then be purified further if required by, for example, recrystallisation.

Alternatively, the product can be crystallised directly from the reaction solvent. In this case, the preferred reaction solvents are aliphatic hydrocarbons. In a preferred embodiment of the invention, the same solvent is used in steps a) and b) of the process and in the final purification.

The following Examples illustrate the invention.

The products were analysed by Gas Chromatography using an Agilent gas chromatograph with a Chrompack CP Sil 5 CB column (50 metres, 0.32 mm ID and 0.1 μ m film thickness) with helium as carrier, split injection at 15 psi. Injection temperature 300°C detector 325°C and a detector gas composition of hydrogen 30 ml/min, air 350 ml/min and helium at 30 ml/min). The oven temperature profile was: initial temp 50°C, initial time 6 mins then heating rate 10°C min to 120°C and hold for 3 mins then ramp to 240°C at 25°C/min. Hold for 8 minutes then ramp to 300°C at 50°C and hold for 6 minutes to burn off the column.

Using these conditions, the following retention times were observed:

(S)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (gamma-cyhalothrin) 27.4 mins

(R)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate 27.0 mins

EXAMPLE 1

Preparation of 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane carboxylic acid chloride

A 1 litre dry, clean jacketed split reaction vessel equipped with agitator, thermometer, condenser, nitrogen blanket and vent to a scrubber system was charged with toluene (450ml) and agitated whilst 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane carboxylic acid (89.4gm = 0.369mol) was added followed by triethylamine (0.21gm = 2.1mmol). The reaction mixture was then heated to 45°C,

using oil circulation on the jacket, and thionyl chloride (62.0gm = 0.52mol) was then charged over 105 minutes maintaining on temperature. The reaction mass was then agitated for 5 hours at 45°C then tested by GLC for completion of reaction showing 2% residual acid. A further addition of thionyl chloride (4.4gm = 37mmol) was then made and the reaction mass allowed to cool with stirring overnight. The following day, residual thionyl chloride, dissolved sulphur dioxide and hydrogen chloride gases were removed by distillation of about 320ml toluene under vacuum. GC, GCMS and NMR analysis of the product were consistent with the structure of the acid chloride (IIIa). Yield, 175gm of a 54% solution of the acid chloride in toluene, 97% theory. $\alpha_D = +46^\circ$ (c= 0.012, DCM).

Example 2

Thermal coupling of ((1R,3S)-3-((Z)-2-Chloro-propenyl)-2,2-dimethyl-cyclopropanecarbonyl chloride to (S)-3-phenoxybenzaldehyde cyanohydrin with distillative removal of HCl and completion with pyridine.

The acid chloride (II) (5 gm 23 millimol) and cyclohexane (25 ml) were added to a dry 100 ml 3 necked round bottomed flask fitted with magnetic stirrer bar, short path distillation equipment (vented to a caustic scrubber system), thermometer and nitrogen blanket. The reactor contents were agitated and heated to 80°C. Distillation was started and the S - cyanohydrin (5.06 gm @ 90% = 20 millimol), dissolved in a little cyclohexane, was then added over approximately 1 hour. Cyclohexane was then continually added at the same rate as the loss of cyclohexane by distillation. After 3.5 hours, GC analysis showed that most of the acid chloride had been consumed. A further charge of acid chloride was made (0.35 gm 1.3 millimol) and the reaction mixture allowed to cool and stir overnight. A further addition of acid chloride (0.7 gm 2.6 millimol) was made and refluxing continued for 21hrs after which time there was still 1.9area% acid chloride in the reaction mass.

Pyridine (0.05 gm 0.6 millimol) and S - cyanohydrin were added (0.314 gm 1.3 millimol), and the reaction mass was refluxed for 3 hrs then allowed to cool to room temperature. GC analysis showed the acid chloride level to be 0.1%. The reaction mass was then worked up by the addition of hexane (40 ml) which promoted crystallisation on stirring. The resultant white solid was separated from the solvent by filtration and

washed with hexane (2 x 5 ml), water (5 ml) and hexane (5 ml) and pulled dry to give a white solid (1.4 gm). The organic phase was washed with 2 molar hydrochloric acid (20 ml), water (20 ml) and brine (20 ml). Both the solid product and organic phase were then analysed by GC. The product in both solid form and in solvent solution had a ratio of (S)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate to (R)- α -cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate of 95:5.

Example 3

Thermal coupling of ((1R,3S)-3-((Z)-2-Chloro-propenyl)-2,2-dimethyl-cyclopropanecarbonyl chloride to (S)-3-phenoxybenzaldehyde cyanohydrin with distillative removal of HCl.

The S - cyanohydrin (1 gm @ 90% = 4 millimol) was charged to a clean dry 3 necked round bottomed flask fitted with magnetic stirrer bar, short path distillation equipment (vented to a caustic scrubber system), thermometer and nitrogen blanket.

Cyclohexane (15 to 20 ml) was then added to the reactor agitation and the nitrogen blanket started at 20°C. The S - cyanohydrin was a slurry in the system at this temperature. The slurry was agitated and heated 80°C until the cyclohexane started to distil. At this point the acid chloride (1.24 gm 4.8 millimol) dissolved in cyclohexane (15 ml) was added, dropwise, to the reactor over 1 hour trying to balance the addition rate with the cyclohexane distillation rate. The addition of the acid chloride was sub-surface via a syringe pump fitted with a Teflon syringe. Once the addition was complete the distillation was continued replacing the distilled cyclohexane with fresh solvent. Reaction progress was monitored by GC. After completion of addition, there was 29area% acid chloride, 24area% cyanohydrin and 44area% gamma-cyhalothrin present (96:4 ratio of α -S to α -R diastereomers). After 2.5 hours a further addition of S - cyanohydrin (0.1 gm = 0.4 millimol) was made and the distillation continued for a further 1 hr after which time there was still 7.3area% acid chloride remaining. The reaction mass was then cooled to room temperature and left, without agitation, overnight under nitrogen. The following day the reaction mass was re-heated to 80°C and a further addition of S - cyanohydrin (0.1 gm = 0.4 millimol) made followed by 3

hours of distillative reaction and finally cooling and bottling off. Analysis of the reaction showed that the diastereoisomer ratio was 95:5.

Example 4

- 5 Further runs were performed and the results are given in Table I.

TABLE I

Coupling of ((1R,3S)-3-((Z)-2-Chloro-propenyl)-2,2-dimethyl-cyclopropanecarbonyl chloride with (S)-3-phenoxybenzaldehyde cyanohydrin

Experiment Number	Scale Gm of Acid Chloride	Solvent	Base/Buffer (Base mol ratio)	Reaction Temp °C	Mode of addition	End of reaction Acid Chloride Area %	Product Diastereoisomer Ratio
1	2.0	Toluene	Pyridine (1.1)	-10°C	Acid chloride added to cyanohydrin and then base added	0	92.8
2	0.65	Toluene	Pyridine (1.1)	-10°C	Acid chloride added to cyanohydrin and then base added	0	92.5
3	5.0	Toluene	Pyridine (1.1)	-10°C	Slow base addition to acid chloride + cyanohydrin	0	95.5
4	2.8	Toluene	Pyridine (1.1)	-10°C	Co-addition of acid chloride & base to cyanohydrin	0.3	95.4
5	7.1	Water	NaOH/phosphate	10°C	Co-addition of cyanohydrin and acid chloride with aqueous controlled at pH 7±1	6.8	92.9
6	5.6	Hexane/water	NaOH/phosphate	10°C	Co-addition of cyanohydrin and acid chloride with aqueous controlled at pH 7±1	20.7	88.7

7	3.3	Hexane/water	Sodium tetraborate (1.5)	10°C	Co-addition of cyanohydrin and acid chloride with aqueous at pH 9	0.1	92.6
8	5.6	Hexane/water	NaOH	10°C	Co-addition of cyanohydrin and acid chloride with aqueous controlled at pH 13	27.4	44.4

In Experiments 1-2, the cyanohydrin had an S to S+R ratio of about 92 and in Experiments 3-8 the ratio was 96.2

CLAIMS

1. A process for the preparation of gamma-cyhalothrin comprising steps of a)
chlorinating 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl
5 cyclopropanecarboxylic acid to give 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-
propenyl)-2,2-dimethyl cyclopropanecarboxylic acid chloride and b)
esterifying 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl
cyclopropanecarboxylic acid chloride with the (S)-cyanohydrin of 3-phenoxy
benzaldehyde (III).

ABSTRACT

A process for the preparation of gamma-cyhalothrin comprising steps of a) chlorinating 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl
5 cyclopropanecarboxylic acid to give 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid chloride and b) esterifying 1R *cis*-Z 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid chloride with the (S)-cyanohydrin of 3-phenoxy benzaldehyde (III).

PCT Application
PCT/GB2004/000726

